Presented here is a case of increasing BIS in response to noradrenergic beta receptor stimulation via the administration of isoproterenol while under general anesthesia. The rise in BIS values appeared to have no correlation to the stimulation produced by the procedure. The patient reported no intraoperative recall despite BIS values in the high 70s. This case reinforces that BIS values require interpretation and can only be relevant to the circumstances of the individual case.

Key words: Bispectral index, dexmedetomidine, isoproterenol, radiofrequency ablation.

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45. Myocardial mapping was continued, and the patient was again placed on an isoproterenol infusion. As before, the BIS value was noted to rise. During this time the patient’s BIS value was as high as the mid-70s. This was treated with propofol, fentanyl, and midazolam. Propofol, as high as 240 µg/kg per minute, was required to maintain the BIS value below 60, at which time the patient’s electrocardiogram reverted to supraventricular tachycardia. Isoproterenol was witheld. The patient was successfully cardioverted again. The withdrawal of isoproterenol was again followed by the patient’s BIS value dropping to a low of 5. Propofol was titrated to a BIS value of 45. Myocardial mapping was continued, and the patient was placed on an isoproterenol infusion once again. Because of difficulty in the mapping process, the cardiologist requested the isoproterenol infusion be increased to 2 µg/min. At this time the propofol infusion was at 260 µg/kg per minute with a BIS value of 67.

Dexmedetomidine was added to the anesthetic at a dose of 1 µg/kg over 15 minutes, followed by an infusion of 0.5 µg/kg per minute. The use of dexmedetomidine allowed for the reduction of the propofol infusion to 150 µg/kg per minute. After 90 minutes of both dexmedetomidine and propofol infusing, the BIS values stayed in the mid-50s. Once again the patient experienced supraventricular tachycardia requiring cardioversion. Over the next 105 minutes, this scenario repeated itself twice. Each time the isoproterenol was witheld or added, the BIS value would plummet or rise respectively.

After 10 hours from the time of induction, the ablation process was complete and the case ended. The isoproterenol was discontinued, and, as before, the BIS value plummeted following its withdrawal. The BIS value was now 0. Both the dexmedetomidine and propofol were discontinued, and the patient was allowed to recover over a 45-minute span. Following the return of airway reflexes and BIS values in the low 90s, the patient was extubated. She was then transported to the postanesthesia care unit and admitted to a monitored setting for 24 hours. During this admission the patient had 2 asymptomatic episodes of hypotension (blood pressure, 80/40 mm Hg). Both responded to fluid administration. Aside from the hypotension, the patient had an uneventful hospital admission. The patient was discharged reporting only a headache. No other ill effects from anesthesia were reported.

Discussion

The use of BIS for monitoring neuronal function under general anesthesia has been expanding. Interestingly, so have the reports of altered BIS values in response to drug administration. Hans and colleagues confirmed a paradoxical elevation in BIS values and a deepening of hypnosis with the addition of ketamine to a sevoflurane-based anesthetic. Results regarding the effects of ketamine on BIS were similarly reported by Morioka as well as Hirota. Overestimated BIS values due to muscle activity also have been reported. Vivien et al demonstrated that the administration of neuromuscular blocking agents to sedated intensive care unit patients decreased BIS values and correlated with electromyographic data. Fodale recently summed up the work of Ghoneim regarding the ability of physostigmine and other cholinesterase inhibitors to antagonize the hypnotic effect, resulting in arousal and higher BIS values. Further studies by Meuret et al showed that physostigmine can reverse propofol-induced unconsciousness in human volunteers. Based on his work, Meuret et al concluded that “unconsciousness produced by propofol is mediated, in part, via interruption of central cholinergic muscarinic transmission.”

Perhaps more relevant to our case is the report by Ishiyama and colleagues who demonstrated that the use of ephedrine, an indirect acting noncatecholamine that stimulates alpha and beta receptors, significantly elevated BIS values. Ishiyama and colleagues also reported, in the same study, the lack of effect on BIS with the use of phenylephrine, a noncatecholamine that is a selective alpha, agonist. This report indicates that beta stimulation by ephedrine resulted in a similar elevation of BIS values as we report with the use of the direct beta-stimulating drug isoproterenol.

The ability of isoproterenol to stimulate beta receptors centrally and increase arousal has been supported by research using rodent models. Studies conducted by Berridge and colleagues document noradrenergic beta receptors in the medial septal and medial preoptic area of the locus coeruleus. Stimulation of these receptors exerts wake-promoting actions and overall arousal states in the rat model. Beta stimulation and increased anesthetic requirement should not be surprising. Work by Johansen et al demonstrated a decreased anesthetic requirement and promoted electroencephalogram burst suppression with the use of esmolol, a beta blocking agent.

At the time of this case, it was our impression that the isoproterenol was responsible for the elevations in BIS values. The mechanism was suspected to be an increase in neuronal discharge caused by beta receptor activation. We based our suppositions on the well-established ability of isoproterenol to produce central nervous system stimulation. Agitation and restlessness are common side effects of the use of isopro-
terenol as a bronchial dilator in its nebulized form.\textsuperscript{13}

Isoproterenol, a synthetic catecholamine, is formed by the addition of an isopropyl group to the terminal amine of norepinephrine. Isoproterenol acts on both beta\textsubscript{1} and beta\textsubscript{2} receptors to produce an increase in heart rate, myocardial contractility, and automaticity. Isoproterenol is devoid of alpha activity and is metabolized quickly in the liver by catecholamine O-methyl transferase, therefore requiring an infusion to maintain therapeutic levels.\textsuperscript{13-15}

Based on the assumption of sympathetic feedback it was felt that the addition of dexmedetomidine would be an excellent choice as an adjunct to propofol. Dexmedetomidine was chosen for its alpha\textsubscript{2} stimulating ability. This choice was based on past experience with the alpha\textsubscript{2} stimulant clonidine. More recently, Fehr et al\textsuperscript{16} confirmed clonidine’s ability to decrease BIS values and decrease anesthetic requirements. Dexmedetomidine is highly specific for alpha\textsubscript{2} receptors and is considered a true selective agonist. Dexmedetomidine has dose-related sedative, anxiolytic, analgesic, and anesthetic sparing effects.\textsuperscript{17} Its major site of hypnotic effects is mediated via alpha\textsubscript{2} adrenergic receptors found in the locus coeruleus.\textsuperscript{18} Dexmedetomidine undergoes biotransformation in the liver via the cytochrome P-450 system and has a half-life of 2 hours. It is administered as an intravenous infusion in a loading dose of 1 \(\mu g/kg\) over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 \(\mu g/kg\) per hour.\textsuperscript{19}

**Significance**

In reviewing the literature, there appears to be no reports of correlation between isoproterenol and anesthetic requirements. Nor are there any studies relating isoproterenol to a patient’s level of awareness while under anesthesia. This may be due to 2 factors. Iso- proterenol is now used very infrequently, and the ability to monitor neuronal activities by using the BIS monitors is relatively new.

In light of this case some interesting questions arise. Questions such as can isoproterenol and other drugs that increase neuronal outflow generate consistently higher BIS values? If so, do these elevated BIS values represent an organized or random activity of the central nervous system? And finally, do these elevated BIS values then translate into a greater sense of awareness under general anesthesia. If the answer is yes to any of these questions, we must carefully consider how we use the BIS monitor and how it relates to drug administration for each case.

**REFERENCES**


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